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EXAMINER	
HA, JULIE	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,357	BARU ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-42,45,47,50,53,54 and 57-74* is/are pending in the application.

4a) Of the above claim(s) *45,47,50,53,54,58,69,71 and 72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-42,57,59-68,70,73 and 74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment after FINAL rejection filed March 6, 2009 is acknowledged. Upon reconsideration, the finality sent out on January 6, 2009 is withdrawn, and the case is hereby reopened. The indication of allowability of claims 45 and 53 are hereby withdrawn. Claims 1-27, 43-44, 46, 48-49, 51-52, 55-56 have been cancelled and new claims 58-74 have been added. Claims 28-42, 45, 47, 50, 53-54 and 57-74 are pending in this application. Applicant elected without traverse of species G-CSF for protein and multiple sclerosis as the disease in the reply filed on June 11, 2007. Claims 45 and 53 were inadvertently examined in the previous office action. These claims are drawn to nonelected species. Amended claims 45, 47, 50, 53, 54, 58, 69, 71-72 are withdrawn from further consideration, as being drawn to nonelected species. **Claims 28-42, 57, 59-68, 70, and 73-74 are examined on the merits in this office action**. Non-final office action follows below.

Withdrawn Rejection

1. Claims 28-42, 46-51, 54-56 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description, is hereby withdrawn in view of Applicant's amendment to the claims.

2. Claims 28-32, 36-37 and 39-42 rejected under 35 U.S.C. 102(b) as being anticipated by Baru M (WO 99/55306, filed in the IDS 2/15/2006), is hereby withdrawn in view of Applicant's amendment to the claims.

3. Claims 44, 46-50, 54-56 rejected under 35 U.S.C. 112, first paragraph, as not enabling, is hereby withdrawn in view of Applicant's amendment to the claims. Please note: claims 47, 50, 53-54 are withdrawn from consideration, as being drawn to nonelected species.

Maintained and Revised Rejection

35 U.S.C. 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 28-34, 36-37, 39-42, 57, 59-60, 62, 65, 67-68 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baru M (WO 99/55306, filed in the IDS 2/15/2006).

8. Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles. The particles comprise approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer which carries substantially no net charge. The protein or polypeptide is capable of externally binding the colloidal particles, or is capable of binding polyethylene glycol and is not encapsulated in the colloidal particle (see abstract). Furthermore, the reference teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, binds to membranes comprising phosphatidylcholine:phosphatidylserine (PC:PS); non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V (see p.7, lines 6-12, claims 18-19), which meets the limitations of claims 28-29, 32 and 36-37. The reference teaches the polyethyleneglycol-phosphatidyl ethanolamine (PEG-PE) preparation (see p. 6, lines 19-20), meeting the limitation of claims 33, 60, 62, 65, 67-68. Additionally, the reference teaches distearoyl phosphatidyl-ethanoloamine methyl PEG 2000 (DSPE-PEG 2000), meeting the limitation of claim 34. As defined by

the instant specification, aminopropanediol distearoyl (DS) is an example of carbamate-linked uncharged lipopolymers (see paragraph [0020]). The reference teaches that "the term proteins or polypeptides capable of binding polyethylene glycol includes proteins and polypeptides which bind to PEG or derivatives of PEG by any non-covalent mechanism, such as ionic interactions, hydrophobic interactions, hydrogen bonds and Van der Waals attraction (see p. 7, lines 13-18), meeting the limitation of non-covalent interaction. The reference further teaches that the colloidal particle has a mean particle diameter of between about 0.05 to about 0.4 microns, and approximately 0.1 microns (see claims 2-3), which meets the limitation of claims 30-31, 59, 74. It is noted that claim 30 has been rejected over the prior art, even though the reference does not disclose exact colloidal particle diameter range as claimed. However, both the claims and the reference utilize the term "about" when discussing the colloidal particle diameter. The term "about" allows for some tolerance in the ranges disclosed. In *In re Ayers*, the Federal Circuit held that "at least about 10%" was anticipated by a reference that disclosed "about 8%" because the term "about" allowed for some tolerance. *In re Ayers*, 154 F.2d 182, 185 (Fed. Cir. 1946). Similarly, in Johnson and Johnson v. W.L. Gore & Associates, Inc., the Court allowed for "about 1.2" to be inclusive of 1.0. See Johnson and Johnson v. W.L. Gore & Associates, Inc., 436 F.Supp. 704, 728-729 (Fed. Cir. 1977). Although about has never been confined to specific percentage of variability, the Johnson and Johnson decision at least implies that 16% variability is permissible when "about" is used (1.0/1.2 = ~16.6% variability). Thus, the term "about" implicitly discloses some variability even though the specification may not literally cite

this variability. Thus, the disclosure of a colloidal particle diameter of "about" 0.05 μm encompasses a diameter of "about" 0.03 μm, as claimed. The reference further teaches that the amphipathic lipid is a phospholipid from natural or synthetic sources (see claim 4), which meets the limitation of claims 32, 36. The reference further teaches that the biocompatible hydrophilic polymer is selected from group consisting of polyalkylether, polylactic and polyglycolic acid families, and is a polyethylene glycol (see claims 6-7), which meets the limitations of claims 39-40.The reference further teaches that the polyethylene glycol has a molecular weight of between about 1000 to about 5000 daltons (approximately 2000 daltons) (see claims 8-9), which meets the limitations of claims 41-42. The reference further teaches that "phospholipids used are synthetic and no-toxic, and can therefore, be used in vivo for therapeutic treatment…liposomes do not encapsulate FVIII, so that smaller sized liposomes can be used which have a longer half-life *in vivo*, since they are not removed by the reticuloendothelial system (RES) (see p. 4, lines 1-6). Since non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V, this meets the limitation of other proteins. The reference teaches the treatment of blood disorder, such as hemophilia (see claim 14). The reference teaches all of the active method steps of instant claim 57. The active method steps of instant claim is that a pharmaceutical composition for parenteral administration is administered to a patient, wherein the protein or polypeptide is not encapsulated in the colloidal particles. The reference teaches administration of a therapeutically effective amount of a compound to a patient in need thereof (see claim 14), and defines that "the term therapeutically effective amount is to be understood as

referring to an amount of FVIII which results in a level of FVIII in the bloodstream having a desired therapeutic effect (see p. 4, lines 14-19). The reference further teaches that liposomes containing E-PC/PEG-PE were the most effective since both the initial FVIII activity and the half-life time were higher for this composition than for Kogenate or Kogenate-liposome mixtures where the liposomes were composed of E-PC/PG or E-PC only (see Table 1, p. 11, lines 3-7). Please note, the intended use has not been given any patentable weight, since it does not further limit the compound.

The difference between the reference and the instant claims is that the reference does not teach the protein or polypeptide is selected from the group consisting of Factor VIIa, G-CSF, GM-CSF, interferon-γ, GLP-1 and COPAXONE®.

9. However, it would have been obvious to one of ordinary skill in the art to use other proteins and polypeptides. One of ordinary skill in the art would have been motivated to try other proteins and polypeptides, since Baru reference teaches that the Factor VIII, prothrombin, Factor V and Factor X would be successful, and phospholipids used do not encapsulate FVIII, so that smaller sized liposomes can be used which have a longer half-life *in vivo*. Peglyation of protein is general concept for proteins. Pegylation of protein increases the half-life of the proteins or peptides. One of ordinary skill in the art would be motivated to pegylate or utilize colloidal particles to increase the half-life of the protein. There is a reasonable expectation of success, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide which are similar to FVIII, and include prothrombin, Factor X and Factor V. Additionally, when liposomes do not

encapsulate the protein, then smaller sized liposomes can be used which have a longer half-life in vivo, since they are not removed by the reticuloendothelial system (RES) (p. 4, lines 1-6). Furthermore, the intended use has not been given any patentable weight, since it does not further limit the compound.

Response to Applicant's Arguments

10. Applicant argues that "Baru et al do not teach or suggest a pharmaceutical composition containing Factor VIIa for treating trauma bleeding in hemophilia patients as admitted by the Examiner who indicated claim 45 allowable. Claim 45 is dependent on claim 28 and recites, "[t]he pharmaceutical composition of claim 28, wherein the polypeptide is Factor VIIa, and the composition may be used with inhibitors for the treatment of trauma bleeding in hemophilia patients." Applicant argues that "claim 57 has been amended to delete "Factor VIIa". It is submitted that Baru et al do not teach or suggest a protein or polypeptide selected from the group consisting of G-CSF, GM-CSF, interferon γ, GLP-1 and CAPAXONE®, as recited in claim 57."

11. Applicant's arguments have been fully considered but have not been found persuasive. Please note that Factor VIIa is not an elected species. Pegylation of protein and peptides is general concept in the protein art. Pegylation of proteins and peptides are well known in the art to increase the half-life of peptides and proteins. Baru reference teaches that the Factor VIII, prothrombin, Factor V and Factor X would be successful, therefore, other proteins would necessarily be successful. Baru reference teaches that phospholipids used do not encapsulate FVIII, so that smaller sized

liposomes can be used which have a longer half-life *in vivo.* Therefore, one of ordinary skill in the art would be motivated to pegylate or utilize colloidal particles that do not encapsulate, to increase the half-life of the protein *in vivo.* There is a reasonable expectation of success, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide which are similar to FVIII, and include prothrombin, Factor X and Factor V. Therefore, one of ordinary skill in the art would expect that all proteins can be pegylated.

New Objections

12. Claims 65-66 are objected to for the following reasons: Claim 65 is dependent on claim 63. Claim 63 is dependent on claim 61, and recites, "wherein the biocompatible hydrophilic polymer is polyethylene glycol." Claim 61 is dependent on claim 60, and recites, "wherein the amphipathic lipid is aminopropanediol distearoyl (DS). Claim 60 recites, "wherein the amphipathic lipid is selected from the group consisting of phosphatidylethanoleamine (PE), a carbamate-linked uncharged lipopolymer and aminopropanediol distearoyl (DS)." Claim 65 recites, "wherein the amphipathic lipid is selected from the group consisting of phosphatidylethanolamine (PE), a carbamate-linked uncharged lipopolymer, and aminopropanediol distearoyl (DS)." Claim 66 recites, "wherein the amphipathic lipid is aminopropanediol distearoyl (DS)." Since claim 65-66 depend on claims that already have recited that amphipathic lipid is aminopropanediol distearoyl (DS) (see claim 61), claims 65-66 do not further limit claims 60-61 and 63.

13. Claims 67-68 are objected to for the following reasons: Claim 67 recites, "The pharmaceutical composition of claim 65, wherein the biocompatible hydrophilic polymer is selected from the group consisting of polyalkylether, polylactic and polyglycolic families." Claim 68 recites, "The pharmaceutical composition of claim 67, wherein the biocompatible hydrophilic polymer is polyethylene glycol." Claim 65 is dependent on claim 63, and claim 63 recites, "The pharmaceutical composition of claim 61, wherein the biocompatible hydrophilic polymer is polyethylene glycol." Therefore, claims 67-68 do not further limit claim 63.

TRADEMARK

14. The use of the trademark COPAXONE® has been noted in this application throughout the specification, for example, paragraph [0016] of instant specification US 2007/0167359 A` and claims, for example, 28, 47, 50, 53, 57, 59, 64, 73-74. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

New Rejection

35 U.S.C. 112, 2nd

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 62, 63, 67, 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

17. Claim 62 recites the limitation "the biocompatible hydrophilic polymer" in the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 62 is dependent on claim 60, and claim 60 recites, "The pharmaceutical composition of claim 59, wherein the amphipathic lipid is selected from..." Claim 60 does not recite any biocompatible hydrophilic polymer. Therefore, there is lack of antecedent basis.

18. Claim 63 recites the limitation "the biocompatible hydrophilic polymer" in the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 63 is dependent on claim 62, and claim 62 is dependent on claim 60. Claim 60 recites, "The pharmaceutical composition of claim 59, wherein the amphipathic lipid is selected from..." Claim 60 does not recite any biocompatible hydrophilic polymer. Therefore, there is lack of antecedent basis.

19. Claim 67 recites the limitation "the biocompatible hydrophilic polymer" in the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 67 is dependent on claim 65, and claim 65 recites, "The pharmaceutical composition of claim 63, wherein the amphipathic lipid is selected from..." Claim 65 does not recite any biocompatible hydrophilic polymer. Therefore, the claim lacks antecedent basis.

20. Claim 68 recites the limitation "the biocompatible hydrophilic polymer" in the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 68 is dependent on claim 67, and claim 67 is dependent on claim 65. Claim 65 recites, "The

pharmaceutical composition of claim 63, wherein the amphipathic lipid is selected from..." Claim 65 does not recite any biocompatible hydrophilic polymer. Therefore, the claim lacks antecedent basis.

Rejection-35 U.S.C. § 112, 1st

21. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

22. Claim 64 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention.

The claims are drawn to a pharmaceutical composition for parenteral administration, comprising a therapeutically effective amount of a protein or polypeptide selected from…and one or more colloidal particles comprising approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer, wherein the protein or polypeptide is non-covalently bound to one or more colloidal particles. The claim in question does not recite a “is not encapsulated in the one or more colloidal particles”.

Lack of Ipsis Verbis Support

23. The specification is void of any literal support for the “encapsulated in the one or more colloidal particles” claimed. In the context of encapsulated, the words “encapsulate” and “enclosed” and “entrapped” were searched. The word "entrapped" within the liposome is present in the specification; however, this is relating to a US Patent No. 5,013,556 and the drug compound is entrapped within the liposome. The words "encapsulate" and "enclosed" are not found anywhere in the specification. Throughout the specification discloses drug compounds “not encapsulated in the colloidal particle”. The specification does not disclose “encapsulated in the colloidal particle”.

Lack of Implicit or Inherent Support

24. “While there is not in *haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure.” See MPEP 2163. Thus support can be furnished implicitly or inherently for a specifically claimed limitation. However, the specification lacks any implicit or inherent support for the claimed “encapsulated in colloidal particles”. As explained supra, there is no support for any concept of “encapsulated in colloidal particles” in the specification. Since the limitation “is not encapsulated in colloidal particles” have been removed, this broadens the claims to include those encapsulated in colloidal particle. Therefore, the removal of recitation "not encapsulated in colloidal particles" can be interpreted as any drugs that are encapsulated in colloidal particles.

Rejection-35 U.S.C. 102

25. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

26. Claim 64 is rejected under 35 U.S.C. 102(b) as being anticipated by Allen et al (US Patent No. 5,527,528).

27. Allen et al teach a method of attaching a targeting protein to a polyethylene glycol (PEG) coated liposome by non-covalent binding to the outer surface of the liposome (see FIG 1A; Col. 4, lines 20-27), by conjugating the antibody to a spacer chain such as PEG (see FIG 2B; Col. 4, lines 40-50), or by biotinylation of the antibody and specific, high affinity, non-covalent binding to avidin that is bound to the liposome surface (see FIG 1C; Col. 2, lines 32-42) and Col. 9, lines 55-67; FIG 5, Col. 17, lines 25-55). Allen teaches a pharmaceutical composition comprising a therapeutically effective amount of a protein and neutral colloidal particles that are approximately 1-20 mol percent of an amphipathic lipid derivatized with PEG (see Col. 8, lines 57-59; Col. 9, line 20). Additionally, the reference teaches that liposome compositions are typically prepared with lipid components present in a molar ratio of about 30-75% vesicle-forming lipids, 25-40% cholesterol, 1-20 % polymer derivatized lipid, and 0.01-10 mole percent of lipid derivatized employed for antibody coupling. One exemplary liposome formulation includes hydrogenated soy phosphatidylethanoloamine (HSPE), cholesterol (CH), DSPE-PEG at a molar ratio of 2:1:0.1 (see Col. 8, lines 57-64). The protein is a

targeting antibody that is capable of externally binding the colloidal particle (see FIG 5, Col. 2, lines 32-42; Col. 9, lines 55-67). Allen teaches that the PEG may have a molecular weight of about 1,000-10,000 Daltons, which fully encompasses the molecular weight ranges of present claim 64. The reference further teaches liposome-entrapped compounds, such as peptide hormones, vasopressin, cytokines (interferons alpha, beta, gamma), interleukins and colony stimulating factors (macrophage, granulocyte, granulocyte and macrophage), viral or bacterial vaccines and so one (see Col. 7, lines 18-28). Therefore, the reference anticipates instant claim 64.

35 U.S.C. 103

28. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

29. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

30. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

31. Claims 28-42, 57, 59-67, 70, 73-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baru M (WO 99/55306, filed in the IDS 2/15/2006) in view of Martin et al (US Patent No. 5,225,212) and Zalipsky S (US Patent No. 6,586,001).

32. The teachings of Baru et al are described, supra. The difference between the reference and the instant claims is that the reference does not teach polypeptides Factor VIIa, G-CSF, GM-CSF, interferon-γ, GLP-1 and COPAXONE®, Cholesterol, and aminopropanediol distearoyl (DS) as amphipathic lipid.

33. However, Martin et al teach a liposome composition for extended release of a therapeutic compound in to the bloodstream (see abstract). The liposomes are composed of vesicle forming lipids (phospholipids, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidic acid (PA), phosphatidylinositol (PI) and the like) (see Col. 5, lines 61-66). The reference further teaches that the liposomes are between 1-20 mole percent of vesicle-forming lipid derivatized with hydrophilic polymer, having sizes in a selected size range between 0.1 and 0.4 microns, and contain the therapeutic compound in liposome-entrapped form (see abstract). The reference teaches that a biocompatible hydrophilic polymer is PEG having a molecular weight

between about 1,000-5,000 daltons, and the polymer is derivatized with the polar head group of phospholipids, such as PE (see Col. 3, lines 1-16 and claims 5 and 6). The reference teaches that these are readily water soluble, can be coupled to vesicle-forming lipids, and are tolerated in vivo without toxic effects (see Col. 5, lines 39-43). The reference further discloses that PEG-liposome has a longer retention time in the blood than the conventional liposomes (see Col. 4, lines 44-46 and Figure 9). The reference teaches that the composition is intended for intravenous administration and the polypeptide may be a peptide or protein, such as superoxide dimutase, interferons (alpha, beta, and gamma)…colony stimulating factors (M-CSF, G-CSF, GM-CSF) (see Col. 3, lines 17-41 and claim 9). The reference further teaches supplementation of cholesterol in the composition (see Table 3 and 5). The reference teaches that Cholesterol may be less tightly anchored to a lipid bilayer membrane, particularly when derivatized with a high molecular weight polyalkylether, and therefore be less effective in promoting liposome evasion of the RES in the bloodstream (see Col. 6, lines 3-9). Martin teaches that other lipid components, such as cholesterol, are also known to contribute to membrane rigidity and stability in lipid bilayer structures (see Col. 6, lines 32-35).

34. Furthermore, Zalipsky teaches liposomes containing PEG-substituted neutral lipopolymers provide similar circulation times to liposomes incorporating conventional, negatively charged PEG-substituted phopholipids. Further, the reference teaches that use of the uncharged lipopolymers can also present advantages in terms of interactions with cell surface and reduce leakage of charged substances (see abstract). The

reference teaches different types of lipids (see Col. 3, lines 1-24) and the synthesis of PEG-Aminopropanediol distearoyl (see Example 1A).

35. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru et al, Martins et al and Zalipsky patents, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V. Martin et al teach G-CSF, M-CSF, GM-CSF, and other proteins that are incorporated with the liposomes. Zalipsky teaches liposome containing PEG-substituted neutral lipopolymers containing proteins, antibodies, vitamins and so on, and the PEG-DS lipopolymer. One of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts all teach therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which have a longer half-life in vivo, because they are not removed by the RES (see p. 4, lines 1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated in vivo without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. Zalipsky teaches that the neutral lipopolymers provide advantages in terms of interactions with

cell surfaces. Since Baru teaches DSPE-PEG lipopolymer was successful and Zalipsky teaches PEG-DS lipopolymer was successful, one of ordinary skill in the art would have been motivated to try DS, since DS and DSPE belong to the same family, and expect that DS would be successful. Furthermore, pegylation of protein is general concept in the protein arts. There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have a longer half-life in vivo. There is a reasonable expectation that other proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide.

Conclusion

36. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Julie Ha/
Examiner, Art Unit 1654